A Progress Report for Phase I Activities Submitted to the

U.S. Department of Energy
Nuclear Engineering Education Research (NEER) Program

By the

University of Florida
Gainesville, Florida 32611

For a project entitled

Advances in Photon and Neutron Skeletal Dosimetry Through NMR Microscopy

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Research Goals and Project Task Objectives

The long-term goals of this project are to: (1) develop detailed 3D models of electron and charged particle transport within trabecular bone taken from various skeletal sites, subject ages, and both sexes, and (2) to extend current Reference Man skeletal dosimetry models to more clinically relevant patient populations. **Task A – Refinement of 200-MHz NMR Imaging Techniques.** ***Objective:*** To establish optimal spatial resolution and sample form needed to construct 3D models of trabecular bone for dosimetry studies. ***Duration:*** Year 1

Task A.1 Investigation of Optimal Spatial Resolution Using a Synthetic Model of Trabecular Bone

In this task, a computer model of a cubical section of trabecular bone, 2.2 x 2.2 x 2.2 cm^3 in size, was constructed. Within an interior 1.6 x 1.6 x 1.6 cm^3 region of interest (ROI), a random array of simulated spherical marrow cavities was placed. The distribution of sphere radii were generated according to the probability density function:

$$P(r) = P_m e^{-P_m r} \qquad (1)$$

where r is the sphere radius and P_m is a fitting parameter that allows changes to the average value of the distribution. The value of P_m found to give the best fit to the Spier's marrow chord distribution (the distribution currently in use in clinical dosimetry and measured some 30 years ago via optical scanning of a 44-year-old male [see original proposal]), was 44 cm^{-1}. The bone trabeculae in the model are taken to be the spaces between non-overlapping spheres within the bone cube. As shown in Figs. 1 and 2, the distributions give by Eq. 1 were found to give a model reasonably consistent with that of the Spier's distributions for the cervical vertebrae for Reference Man (see Figs. 1 and 2).

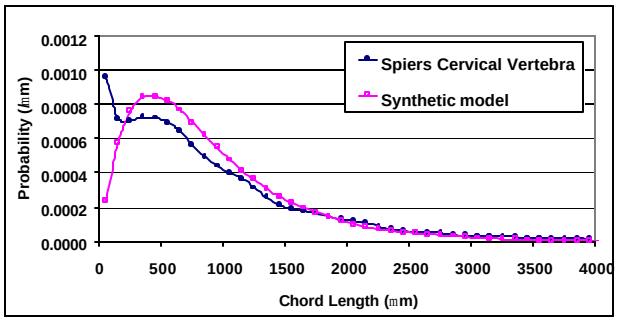

Fig. 1. Marrow Chord Distributions

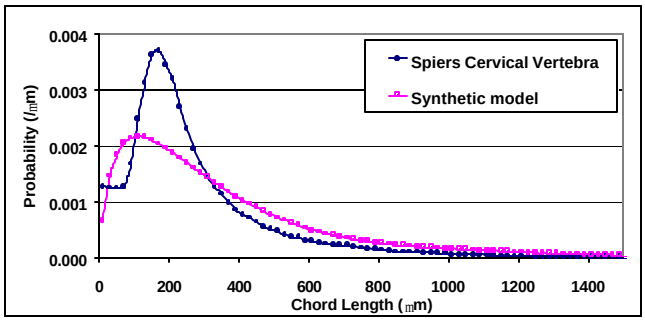

Fig. 2. Bone Trabeculae Chord Distributions

A series of computer codes were subsequently created to simulate NMR images of the synthetic bone cube. For each simulated image, the volume fraction of bone or marrow was assessed through both analytic and Monte Carlo techniques. If the volume fraction of bone exceeded 50%, the entire voxel was segmented as a bone voxel; otherwise, the entire voxel was segmented as a marrow voxel. Nineteen different voxel sizes were created ranging from 1mm per dimension to 16 μm per dimension. Figs. 3 and 4 show the variation of the total marrow volume fraction and the trabecular surface area as a function of voxel resolution. The horizontal line indicates the "true" value within the synthetic bone cube. Note that one can accurately measure the marrow fraction even at relatively large voxels of 250 μm (current imaging at 4.7 T achieves a resolution of between 60 and 80 μm). Nevertheless, due to the voxelized nature of the simulated NMR images, the trabecular surface area is initially underestimated at poor image resolutions (large voxel sizes) due to the loss of trabecular connectivity. As the resolution improves, one increasingly approaches to the "true" surface area. However, at resolutions below 300 μm, an increasingly higher overestimate of the bone surface area results. This error was found only to have a significant impact on dosimetry results for cross region irradiation with low-energy electrons.

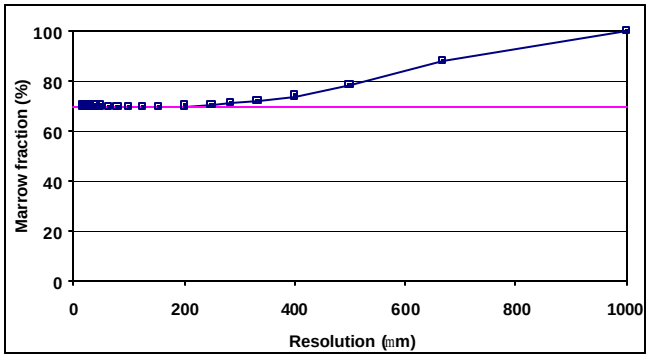

Fig. 3. Marrow Fraction versus Image Resolution

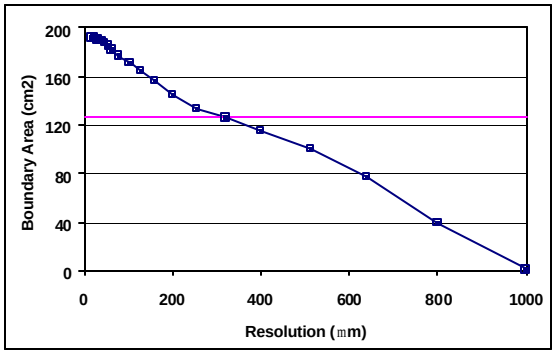

Fig. 4. Bone Surface Area versus Image Resolution

For each of the 19 voxelized images, EGS4 electron transport simulations were conducted simulating a uniform marrow source of monoenergetic electrons. The absolute difference in the absorbed fractions between the segmented image and the reference image ($AF_{segmented}$ - $AF_{reference}$) are plotted in Fig. 5a for the marrow as the target region and in Fig. 5b for the bone trabeculae as the target region. For electron energies greater than 400 keV, these figures show that with increasingly smaller voxel sizes (improved image resolution), one approaches accurate dosimetry for both the self-dose to the marrow and the cross-dose to the bone trabeculae. At these energies, an resolution of only ~150 μm is needed for very accurate dosimetry. This resolution is significantly higher than that currently

achievable on the UF Brain Institute's 4.7 T NMR spectrometer. For lower energy electrons, the error in the surface area presented to the electrons within the voxelized image results in an underestimate of the self-dose to marrow and a corresponding overestimate of the cross-dose to bone. Nevertheless, the magnitude of these errors in relatively small. Still, we are currently investigating methods of correcting doses at low electron energies within our NMR images of trabecular bone.

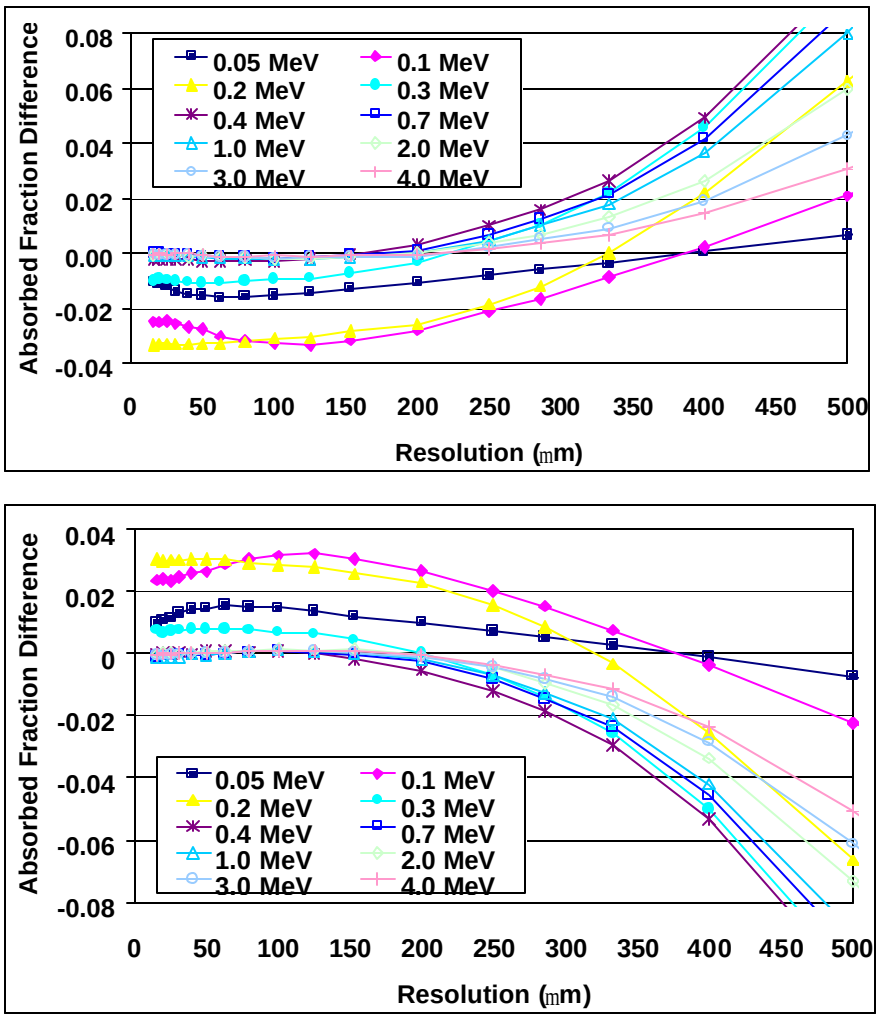

Fig. 5

Absorbed fraction differences between the reference value (obtained within the mathematical sample) and results obtained within the segmented images. The source of radiation is monoenergetic electrons within the marrow cavities. Target regions considered are (a) the marrow cavities, and (b) the bone trabeculae.

(a)

(b)

Task A.2 Investigation of Optimal Image Pulse Sequence and Sample Size

Other efforts within Year 1 included a comprehensive study of pulse sequence and sample size requirements for NMR microscopy of our trabecular bone samples. Through a trail-and-error process, we have settled on a 3D spin-echo pulse sequence on the 4.7 T NMR spectrometer at the UF Brain Institute's Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility. The full procedure for sample harvest and imaging is as follows. (1) Samples are harvested from cadaver sources. To date, 22 bone sites have been harvested from three subjects: a 51-year male, a 82-year

female, and a 86-year female. The older female was substantially smaller in frame that the 82-year female. (2) CT scans are performed for each bone site. The purpose of this step is twofold. First, the 3D images allow one to view the internal trabecular structure of the bone site which aids in deciding where to make bone cube cuts for NMR imaging samples. Second, the 3D CT images allow one to better construct a full macroscopic model of the bone site indicating the 3D shape of the trabecular regions and the thicknesses of the cortical bone cortex needed for subsequent 3D electron transport. (3) Bone cubes are then cut. We are currently cutting samples roughly 2 cm x 1.5 cm x 1.5 cm dimension. (4) Next, the bone cubes are subjected to chemical digestion of the marrow tissues. If marrow intact samples are used (for comparison purposes) this step is skipped. (5) The samples are then immersed in Gd-doped water and imaged on the 4.7 T system. A 3D spin-echo pulse sequence is employed using a repetition time TR=1500 ms for marrow intact samples and TR=200 ms for marrow digested samples. The echo time TE = 11-13 ms for both. An image matrix of 512 x 256 x 256 is used. Marrow-intact samples are imaged for ~15 hours with one imaging average. Marrow-digested samples are images for ~7 hours with 2 averages taken. (6) The next step is to utilize in-house codes for image processing including image segmentation (creating a binary image of marrow and bone voxels) and image filtering (removal of stray voxels attributed to noise in the image system). (7) The final step is a coupling of the image to the EGS4 transport code for particle transport.

Task B - Advanced Progress

Accelerated progress has been achieved for some of the tasks originally scheduled to begin in Year 2. These tasks include the development of macroscopic transport models of the thoracic vertebrae and the femur head. Current work is progressing on a model of the cranium. A new task has also been initiated in gathering data on the histology of normal marrow tissues. In the past, all bone marrow dosimetry models using in clinical and health physics dosimetry have treated the marrow space as a single target. It is well known that marrow tissues include an active component (red marrow) and an inactive component (yellow marrow). Histological definitions of inactive marrow are the adipocytes or fat cells which accumulate with age in the trabecular marrow spaces. We have initiated a new task to characterize the spatial distribution of these fat cells within normal bone from bone marrow samples. Parameters to be characterized include the distribution of fat cells per cluster, the spatial pattern of the clusters (near the center of the marrow cavity or near the bone trabeculae), and the percentage of trabecular bone surface covered. The latter quantity may be significant in that current health physics models allow 50% of energy deposition to marrow for bone-surface depositions of alpha-particle emitting radionuclides. If a “first-fat layer” is seen, then the true absorbed fraction to active marrow

may be in fact zero, significantly increasing the annual limit on intact of bone-seeking radionuclides for occupational workers in DOE clean-up activities. Finally, we have created preliminary models of trabecular bone which are segmented into three, rather than two, tissues - bone, active marrow, and inactive marrow. The latter is achieved through declaring some of the marrow voxels to be fat cells or fat cell clusters. Clinically and operationally, this refinement to the model will be significant in that the fat percentage of marrow varies with bone site and with subject age.

Publications

Voxel Size Effects in 3D NMR Microscopy Performed for Trabecular Bone Dosimetry
DA Rajon, DW Jokisch, PW Patton, AP Shah, and WE Bolch
Medical Physics (resubmitted with minor revisions)

Chord Distributions Across 3D NMR Images of a Human Thoracic Vertebra
DW Jokisch, PW Patton, DA Rajon, BA Inglis, and WE Bolch
Medical Physics (submitted)

Beta-Particle Dosimetry of the Trabecular Skeleton Using Monte Carlo Transport in Voxelized Images
DW Jokisch, LG Bouchet, PW Patton, DA Rajon, and WE Bolch
Medical Physics (submitted)

Spatial Distribution of Adipocytes in Marrow Tissues and Their Impact of Skeletal Dosimetry
AP Shah, PW Patton, DA Rajon, and WE Bolch
Health Physics (in preparation)

Impact of Marrow Cellularity on Absorbed Fractions for Electron Irradiation of Trabecular Bone
AP Shah, PW Patton, DA Rajon, and WE Bolch
J. Nucl. Med. (in preparation)

Abstracts Presented at National Meetings

DA Rajon, DW Jokisch, PW Patton, AP Shah, and WE Bolch, "3D NMR Microscopy in Skeletal Dosimetry: A Study of Voxel Size Effects on Dose Estimates", World Congress on Medical Physics and Biomedical Engineering, Chicago, Illinois, July 23-38, 2000.

WE Bolch, DW Jokisch, PW Patton, DA Rajon, and LG Bouchet, "Investigation of NMR Microscopy for Use in Skeletal Dosimetry Models", 47th Annual Meeting of the Society of Nuclear Medicine, St. Louis, Missouri, June 3-7, 2000, Supplement to *J. Nucl. Med.* **41** 83P (No. 326) (2000).

W. E. Bolch, D. W. Jokisch, P. W. Patton, L. G. Bouchet, D. Rajon, B. A. Inglis, and S. L. Myers, "NMR Microimaging of Trabecular Bone: A New Tool for the Development of Bone Dosimetry Models", 43th Annual meeting of the Health Physics Society, Minneapolis, Minnesota, July 12-16, 1998.

AP Shah, PW Patton, DW Jokisch, DA Rajon, and WE Bolch, "Geometrical Distribution of Adiposites within Normal Bone Marrow: Considerations for 3D Skeletal Dosimetry Models", 44th Annual Meeting of the Health Physics Society, Denver, Colorado, June 25-29, 2000, Supplement to *Health Physics*, **78** S100 (2000).

DA Rajon, PW Patton, A Shah, WE Bolch, "Surface Error Effects of 3D NMR Images on Monte Carlo Trabecular Bone Dosimetry Calculations", 44th Annual Meeting of the Health Physics Society, Denver, Colorado, June 25-29, 2000, Supplement to *Health Physics*, **78** S121 (2000).

PW Patton, DW Jokisch, DA Rajon, A Shah, and WE Bolch, "Introduction of Marrow Cellularity in 3D Electron Simulations in Trabecular Bone", 44th Annual Meeting of the Health Physics Society, Denver, Colorado, June 25-29, 2000, Supplement to *Health Physics*, **78** S100 (2000).

DW Jokisch, PW Patton, DA Rajon, A Shah, and WE Bolch, "The Effects Of The Bone-Marrow Interface In Trabecular Bone Dosimetry of Beta-Particles Utilizing Voxel-Based Transport", 44th Annual Meeting of the Health Physics Society, Denver, Colorado, June 25-29, 2000, Supplement to *Health Physics*, **78** S121 (2000).

PW Patton, DW Jokisch, DA Rajon, EJ Eschbach, DL Wheeler, SL Myers, and WE Bolch, "Comparison of Trabecular Chord Length Distributions Obtained from Nuclear Magnetic Resonance Imaging and Optical Microscopy", 44th Annual Meeting of the Health Physics Society, Philadelphia, Pennsylvania, June 27 - July 1, 1999.

DA Rajon, DW Jokisch, PW Patton, LG Bouchet, and WE Bolch, "Assessment of Minimum Voxel Size for Trabecular Bone NMR Imaging for Dosimetry Calculations", 44th Annual Meeting of the Health Physics Society, Philadelphia, Pennsylvania, June 27 - July 1, 1999.

DW Jokisch, PW Patton, LG Bouchet, and WE Bolch, "Monte Carlo Electron Transport within Voxels from a Three-Dimensional Image of Human Trabecular Bone", 44th Annual Meeting of the Health Physics Society, Philadelphia, Pennsylvania, June 27 - July 1, 1999.